

REMARKS/ARGUMENTS

Claims 23-28 and 32-37 are active. Claims 1-22, 29 and 31 have been cancelled.

Page 13 of the specification has been amended to refer to version 20 of AL162497 which the specification discloses as having a length of 143,409 bp. The attached Revision History of AL162497 describes several versions of AL162497 that were publicly known prior to this application's filing date. However, only version 20 has the length of 143,409 bp disclosed in the specification. For example, versions 18 and 19 are described as having lengths of 194,498. Accordingly, the original specification unambiguously identifies version 20 of AL162497 and the inclusion of this term on page 13 and in the claims is not new matter. SEQ ID NO: 19 is the complement of SEQ ID NO: 18. Accordingly, both sequences inherently describe the same double-stranded polynucleotide sequence. For simplicity the claims have been revised to describe the locations of the polymorphisms by reference to SEQ ID NO: 18 because this sequence is expressly described by version 20 of AL162497 disclosed on pages 13 and 44 of the specification. The claims have also been amended to replace "drug induced" with "vesnarinone-induced" granulocytopenia. Support is found at least in the Examples. Accordingly, the Applicants do not believe that any new matter has been introduced. Favorable consideration of this amendment and allowance of this application are now respectfully requested.

The Applicants thank Examiner Strzelecka for the courteous and helpful discussions regarding how to unambiguously disclose the locations of the single nucleotide polymorphisms based on the disclosure as filed. In May, the Examiner indicated that the GenBank databases contained multiple versions of the AL162497 accession number disclosed in the specification and that this introduced ambiguity. The Applicants subsequently discussed this issue with the Examiner in June after reviewing different versions of the AL162497 sequence. They indicated that version 20 of this sequence was

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contemporaneous with the filing date of this application and thus was well-known as of the filing date, and that version 20 could be unambiguously distinguished from version 19 and other prior versions because the specification indicated that this sequence is 143,409 bp in length, while other versions do not. The Applicants also pointed out that depending on whether the sense or antisense polynucleotide strand was the reference strand, that complementary bases, e.g., A or T, or C or G, can be used to identify the polymorphisms. The Examiner requested that the Applicants elaborate on these points in their next response and recommend filing an RCE to permit time for a comprehensive review of this matter.

Restriction/Election

The Applicants previously elected with traverse **Group I**, claims 1-8, 14, 15 and 19-22, directed to a method for assessing risk of drug-induced granulocytopenia, and the **species genetic polymorphism (e) (A29793G)**. The requirement has been made FINAL. The Applicants understand that additional species will be rejoined and examined upon an indication of allowability for a generic claim reading on the elected species. The Applicants respectfully request that the claims of the nonelected group(s) which depend from or otherwise include all the limitations of an allowed elected claim, be rejoined upon an indication of allowability for the elected claim, see MPEP 821.04.

Objection

Claim 31 was objected to as to form. This issue is now moot.

Incorporation by Reference

The reference to AL162497 and XM_007095 was objected to as being an improper incorporation by reference under 37 C.F.R. §1.57(b), (c) or (d). The Applicants respectfully

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submit that this issue is moot in view of the revision of the specification to refer to version 20 of AL162497. Moreover these accession numbers were well-known as of the effective filing date of this invention. A patent specification need not teach, and preferably omits, what is well known in the art. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).

The specification now clearly and unambiguously identifies the reference sequence AL162497 (version 20) since this was the only version having 143,409 bp as disclosed at the bottom of page 13 of the specification. Since AL162497 is merely a short-hand designation for the corresponding polynucleotide sequence disclosed by SEQ ID NO: 18, and since the complementary sequence shown by SEQ ID NO: 19 is implicitly described, the Applicants submit that no incorporation by reference has occurred, any more than spelling out a well-known acronym would introduce new matter.

Accordingly, the Applicants respectfully submit that no improper incorporation by reference has been made.

Rejections—35 U.S.C. §112, first paragraph (OA, pages 3 and 5)

Claims 23, 25-27 and 29-31 were rejected under 35 U.S.C. 112, first paragraph, as lacking adequate written description on the ground that the specification as filed did not describe where the polymorphisms of the IRS2 gene are located. The issue is whether the original disclosure discloses the claimed invention as it pertains to the locations of particular polymorphisms correlated with vesnarinone-induced granulocytopenia. As discussed above, the positions of the polymorphisms of the invention are described by reference to AL162497 (version 20) which corresponds to SEQ ID NO: 18.

AL162497 (version 20) is a long polynucleotide sequence of which a portion (base pairs 93,673-126,402) encodes the IRS-2 gene (specification, top of page 14). However, this

sequence is an antisense sequence and thus depicts the antisense nucleotides corresponding to the coding sequence for IRS-2 protein. For example, the start codon in the antisense sequence of SEQ ID NO: 18 appears as (“cat”) at base pair 126,402. The sense version of this codon would be “atg”. Similarly, what is down-stream in the antisense sequence of AL162497 (SEQ ID NO: 18) is upstream in the coding sequence shown by SEQ ID NO: 19.

The polymorphisms described in the claims appear as follows in SEQ ID NO: 18:

(a) an oligonucleotide having a sequence including a genetic polymorphism that is C to A conversion at position 130,474 of SEQ ID NO: 18. Page 14, lines 19-20 disclose the polymorphism C-4587A: a C → A conversion. This is depicted in antisense sequence AL162497 as a G → T conversion at the relative position 4,587 up-stream (bp 130,474) from the antisense start codon at 126,402.

(b) an oligonucleotide having a sequence including a genetic polymorphism that is an AT deletion at positions 128,398-128,399 of SEQ ID NO: 18. Page 14, lines 19-20 disclose the polymorphism AT-2510del: an AT deletion. This is depicted in antisense sequence AL162497 as a TA deletion at the relative position 2,510 up-stream (bp 128,398-128,399) from the antisense start codon at 126,402.

(c) an oligonucleotide having a sequence including a gene polymorphism that is A to C conversion at position 127,051 of SEQ ID NO: 18; Page 14, lines 19-20 disclose the polymorphism A-1164C: an A → C conversion. This is depicted in antisense sequence AL162497 as a T → G conversion at the relative position 1,164 up-stream (bp 127,051) from the antisense start codon at 126,402.

(d) an oligonucleotide having a sequence including a gene polymorphism that is A to G conversion at position of 110,018 of SEQ ID NO: 18; Page 14, lines 19-20 disclose the polymorphism A15780G an A → G conversion. This is depicted in antisense sequence

AL162497 as a T → C conversion at the relative position 15,870 down-stream (bp 110,018)

from the antisense start codon at 126,402.

(e) an oligonucleotide having a sequence including a gene polymorphism that is A to G conversion at position 96,095 of SEQ ID NO: 18. Page 14, lines 19-20 disclose the polymorphism A29793G: an A → G conversion. This is depicted in antisense sequence AL162497 (SEQ ID NO: 18) as a T → C conversion at the relative position 29,793 down-stream (96,095 bp) from the antisense start codon at 126,402.

(f) an oligonucleotide having a sequence including a genetic polymorphism that is C deletion between positions 94,356-94,357 of SEQ ID NO: 18. Page 14, lines 19-20 disclose the polymorphism C31532del. This is depicted in antisense sequence AL162497 (SEQ ID NO: 18) as a G deletion at the relative position 31,532 down-stream (between bp's 94,356-94,357) from the antisense start codon at 126,402.

These polymorphisms are specifically and unambiguously identified by their relative positions with respect to the IRS-2 gene's start codon, see page 14 of the specification. This start codon itself is definitively identified as shown by attachments B at bp 516 which corresponds to the "a" in the start codon "atg". Attachment D also depicts the location of the start codon of this gene in its antisense form.

Thus, as of the filing date of this invention, one of skill in the art would have been able to clearly identify this start codon from publicly available information, including GenBank Accession No. AL162497 and GenBank Accession No. XM_007095. If the Examiner disagrees, the Applicants respectfully request that she explain why the locations of the polymorphisms of the invention could not have been unambiguously identified based on accession number AL162497 (version 20) when read in light of the specification and other publicly available information as of the filing date. In view of the above explanations and the

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revision of the specification to identify GenBank Accession No. AL162497 (version 20) the Applicants respectfully submit that these rejections cannot be sustained.

Rejection—35 U.S.C. §112, first paragraph

Claims 23, 25-27 and 29-31 were rejected under 35 U.S.C. 112, first paragraph, as lacking adequate enablement. This rejection is moot in view of the limitation of the claims to vesnarinone-induced granulocytopenia which is exemplified in the specification.

Rejection—35 U.S.C. §112, second paragraph

Claims 23, 25-27 and 29-31 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite. This rejection is moot in view of the deletion of the language deemed indefinite.

Conclusion

In view of the amendments and remarks above, the Applicants respectfully submit that this application is now in condition for allowance. An early notice to that effect is earnestly solicited.

Respectfully submitted,

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